Inherited mutations impair responses to environmental carcinogens: Cancer prevention in mutation carriers

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Running title:

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Abstract

Some environmental carcinogens may be responsible for a modest increase in the numbers of cancers after years of exposure. Economic or political factors weigh against widespread bans of carcinogens. However, lists of chemicals and agents that cause cancer assume that everyone is equally susceptible to their carcinogenic effects.

Hereditary cancer gene mutations can target specific tissues if they are exposed to a carcinogen and the hereditary deficit impairs normal protective responses. Mutation carriers should then have higher risks for specific cancers caused by specific carcinogens.

For example, it can be predicted that BRCA1 or BRCA2 mutation carriers should be highly susceptible to the carcinogen formaldehyde. High formaldehyde levels can overwhelm normal enzyme detoxification systems or detoxification genes may be inadequate or missing. Formaldehyde that is not detoxified causes strands of DNA to cross-link to each other and to nearby proteins. Carriers of mutations in BRCA1/2 dependent pathways are deficient in the ability to undo these cross-links.

Human myeloid leukemias are linked to formaldehyde. Inherited biallelic BRCA2 gene defects and other defects in BRCA1/2 mediated pathways dramatically increase risks for myeloid leukemia, even among infants. In 12 of 15 studies, heterozygous BRCA1 or BRCA2 mutations increase risks for myeloid leukemias. Moreover, chromosome arms lost in hereditary breast cancers encode enzymes essential for formaldehyde metabolism. BRCA1/2 mutation carriers may reduce their very high cancer risks by lowering their exposure to formaldehyde.

Cancers associated with many other hereditary gene deficits can also be stimulated by distinct environmental hazards. Widespread education could prevent or delay some cancers in mutation carriers.

Background

Formaldehyde is a direct human mutagen and known carcinogen [1-4]. Yet widespread human exposures occur during manufacture and use of resins, particle board, plywood, leather goods, paper, pharmaceuticals, cosmetics, baby products, and food. Latex paint, fingernail cosmetics, tobacco smoking, varnishes, floor finishes, auto exhaust and organic combustion all release formaldehyde. Nearly 5 million tons of formaldehyde were produced in the US in 2003, constituting 5% of gross national product [1] and representing a powerful economic force.

Minimal levels of exposure required to produce cancers and other effects on health. Potentially serious common routes of exposure to formaldehyde include inhalation, from occupational exposure and environment, dermal, from occupational handling, and intramuscular or subcutaneous from vaccines.

Fig. 1 gives minimal levels of inhalation and oral ingestion associated with cancers and other adverse health effects [1-6]. Exposures to 38 ppm may occur in the plastics industry and to 8.3

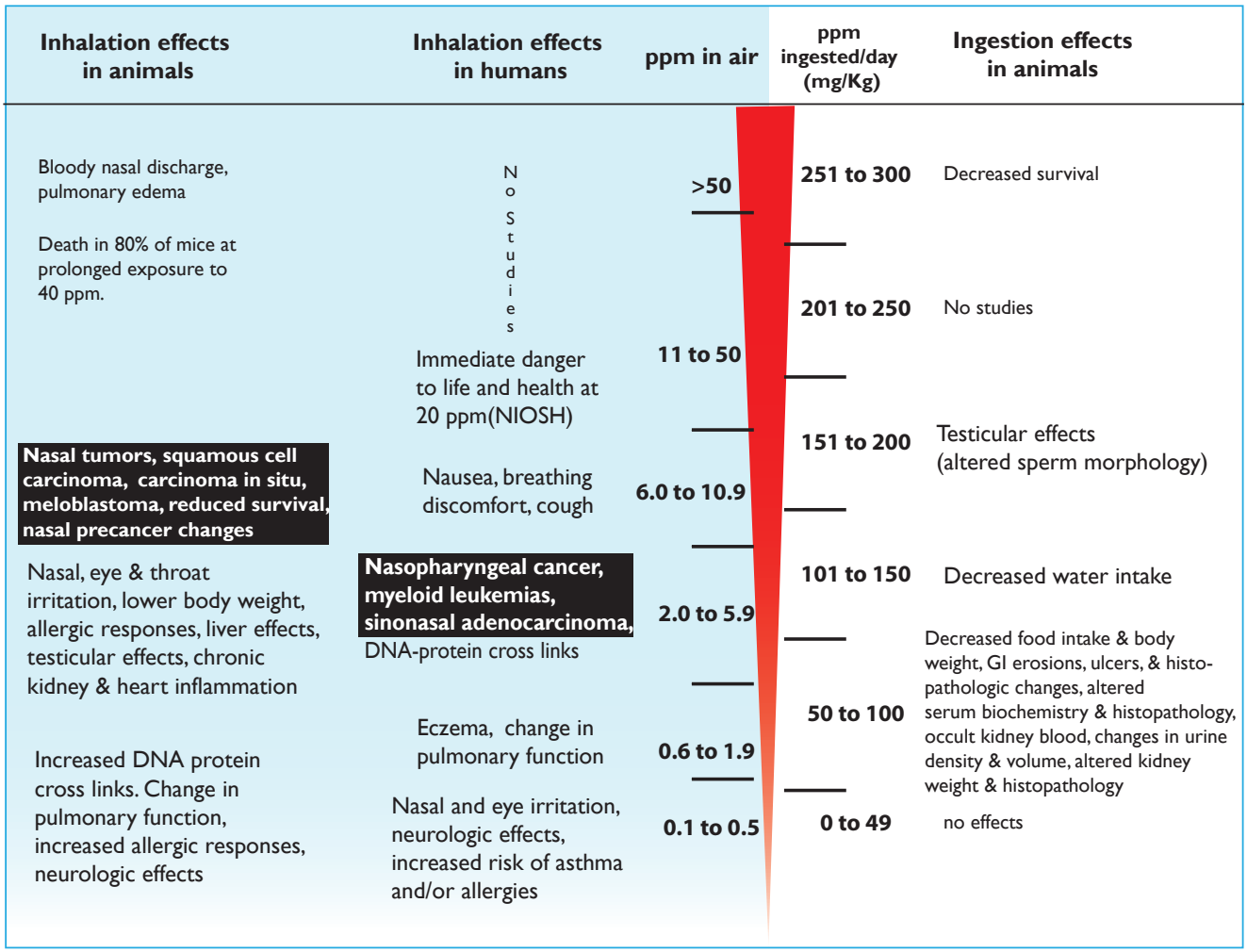

Figure 1. Health effects of formaldehyde exposure in humans and animals [1-6]. Even low level exposures by either inhalation or oral ingestion are associated with several types of cancers and other health effects in normal individuals. The levels shown indicate the lowest levels at which the indicated health effects have been reported. The maximum exposure level of 2.0 ppm in the UK is larger than permissible levels of 0.75 ppm in the USA and 0.1 ppm in Sweden and Germany.

ppm in biology teaching laboratories.

Formaldehyde related cancers. Nasopharyngeal, sinonasal cancer and myeloid leukemia [3, 5] develop at 2 – 5.9 ppm formaldehyde in air (Fig. 1). Nasal epithelium in rats contains stem cells that can produce myeloid white cells [6]. Inhaled formaldehyde might damage these nasal stem cells and cause myeloid leukemia. Individuals with nasopharyngeal cancer have elevated risks for leukemia and other hematological malignancies. Genetic susceptibility loci for nasopharyngeal cancer are all associated with leukemias. Pathogenic mechanisms in hematologic and nasopharyngeal malignancies may have some common features [7].

Mechanisms for formaldehyde induced cancers. Formaldehyde chemically cross-links strands of DNA to each other and to nearby proteins. Carriers of mutations in BRCA1 or BRCA2 genes are deficient in the ability to repair cross-linked DNA. If cells survive without correct repairs, then DNA does not reproduce properly, further mutations become likely and DNA instructions may be misread. Chromosome breaks, gains and losses of chromosomes may result. So BRCA1/2 mutation carriers should be at especially high risk for formaldehyde related cancers.

Formaldehyde itself can exist as polymers of varying length which may form cross linkers with varying reach. The reactions of formaldehyde in DNA-protein mixtures, have been modeled by mixtures of deoxynucleosides and amino acids [8]. Cross-linked products that were chemically irreversible, stable and readily isolated were Cys-CH2-dG, Cys-CH2-dA, and Cys-CH2-dC. The amino acids Histidine and Tryptophan also formed stable cross-links although in lower yield. Three lysine cross-linked products were labile in solution, supporting widely reported reversibility of formaldehyde-induced cross-links between lysine rich histones and DNA [8].

Formaldehyde detoxification by specialized metabolic pathways. Normal metabolism produces formaldehyde and it occurs naturally in plants, fruits, vegetables, animals and seafood. These sources are generally too low to cause permanent harm and are managed by reactions and metabolism within the digestive tract. Formaldehyde is primarily metabolized by glutathione-dependent formaldehyde dehydrogenase (ADH3) and aldehyde dehydrogenases (ALDHs) enzymes in alternative pathways (Fig. 2). Formaldehyde is converted to formate, which is then eliminated in the urine as a sodium salt, broken down to CO_2 and water, or entered into the single-carbon pool.

Deficiencies in any of the enzymes in Fig. 2 would increase damage from reactive oxygen species because unmetabolized formaldehyde causes inflammation. Inhibition of the alcohol (ADH) or aldehyde dehydrogenases (ALDH2) in Fig. 2 has significant impact on formaldehyde toxicity [9]. ADH3 is a member of the alcohol dehydrogenase gene family expressed in many tissues. There are different frequencies of ADH3 alleles among different nationalities.

DNA cross-links, chromosome breaks and chromosome abnormalities are favored by saturating formaldehyde metabolizing pathways with environmental formaldehyde. Exogenous addition products form between formaldehyde and DNA in a highly nonlinear fashion; a 21.7-fold increase in exposure caused a 286-fold increase in exogenous adducts [10]. As shown below, overwhelming formadehyde detoxification is especially likely to cause chromosomal abnormalities in BRCA1/2 mutation carriers [11].

Formaldehyde is more dangerous for some people. One way an inherited cancer

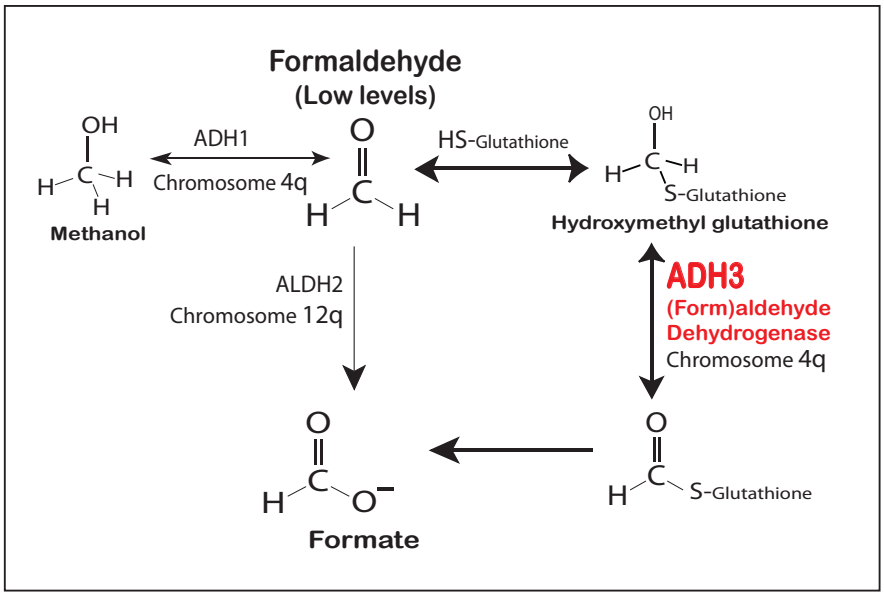

Figure 2 - Formaldehyde detoxification mechanisms. Detoxification of low levels of formaldehyde occurs primarily by a pathway (thicker arrows) involving formaldehyde dehydrogenase (ADH3), an aldehyde dehydrogenase. The pathway converts formaldehyde to formate which is then eliminated in the urine, broken down to CO2 and water or enters the single carbon pool. Alternate, less used pathways are indicated by thinner arrows [9]. Initial detoxification does not involve BRCA1/2. All the genes encoding the ADH enzymes shown are on chromosome 4q which is deleted in 81% of BRCA1 associated breast cancers [11]. Chromosome 12q containing ALDH2 is deleted in 40%. of BRCA1 associated breast cancers [11].

gene mutation may target specific tissues is by increasing cancer susceptibility to environmental carcinogens [12]. This theory can be tested against risks for cancers associated with formaldehyde in BRCA1/2 mutation carriers. Repair of large DNA-protein cross-links caused by formaldehyde requires pathways containing normal BRCA1 and BRCA2 proteins (Fig. 3, [13,14,12]).

Current descriptions of an exquisite specificity for BRCA1 and BRCA2 mutations in causing breast and ovarian cancer require some unique, tissue specific property of BRCA1/2 Loss of BRCA1 mediated inhibition of estrogen receptor signaling could contribute to this specificity [15-17].

An analysis of cancer incidence data found that cancer targets in BRCA1/2 mutation carriers are in fact not exquisitely specific for breast and ovary. There are increased risks for cancers in several other tissues [18]. Moreover, people with compromised pathways containing BRCA1/2 and appropriate risk factors are highly prone to develop cancers mediated by some organ specific inflammatory infections. In these cases, the cancer targets are determined by the organ specific infections and not by the BRCA mutation [12,19]. All tissues are probably unduly susceptible to carcinogens if the carcinogens can exploit the inherited deficit. All tissues have inherited pre-mutated (cancer) stem cells.

Methods

As previously described [12,18,19], the literature was systematically searched for relative risk data on second primary cancers in carriers or likely carriers of mutations in BRCA1/2 genes. Data found in appropriate studies was used directly in Table 1 without combining. No exclusions were made for percentages of mutation carriers in the population, for survival, or for loss of subjects to follow-up.

Testing formaldehyde associated cancer risks in mutation carriers. Of nu-

merous environmental carcinogens that can exploit deficits in the pathways in Fig 3, formaldehyde is among the most abundant and best studied. Six different major and independent criteria (Tests 1-6 below) were devised and used to evaluate risks for formaldehyde associated cancers in mutation carriers (tests 1-6 in results and discussion).

Results and Discussion

Test 1. Mutation carriers have widely varying cancer risks. Female mutation carriers have high risks for breast /ovarian cancer as a group but individual risks within this group vary greatly. There is no single risk associated with BRCA1 or BRCA2 carrier status [20]. Defective BRCA genes increase risks for cancers in organs other than breast and ovary but individual mutation carriers again differ greatly [18]. These results implicate an increased susceptibility in organs exposed to environmental carcinogens and/or deficits in additional genes [12].

Test 2. BRCA1/2 gene mutations are associated with myeloid leukemia. Inherited mutations in BRCA1/2, Fanconi anemia and ATM genes share the ability to compromise the pathways in Fig. 3, hindering complex repairs needed to remove DNA-protein cross-links, and to control aberrant DNA rearrangements [21]. These mutations are all associated with leukemias, especially myeloid leukemias. This association is especially strong for homozygous or biallelic mutations in BRCA2 (Fanconi protein D1). Six children with biallelic BRCA2 mutations all developed leukemia at median age 2.2 years, with 4 of 6 developing acute myeloid leukemia (AML) [22]. Biallelic BRCA2 mutation patients have a 79% cumulative probability of leukemia (primarily AML) by age 10 years ([23] and Table 1).

Homozygous or biallelic mutations

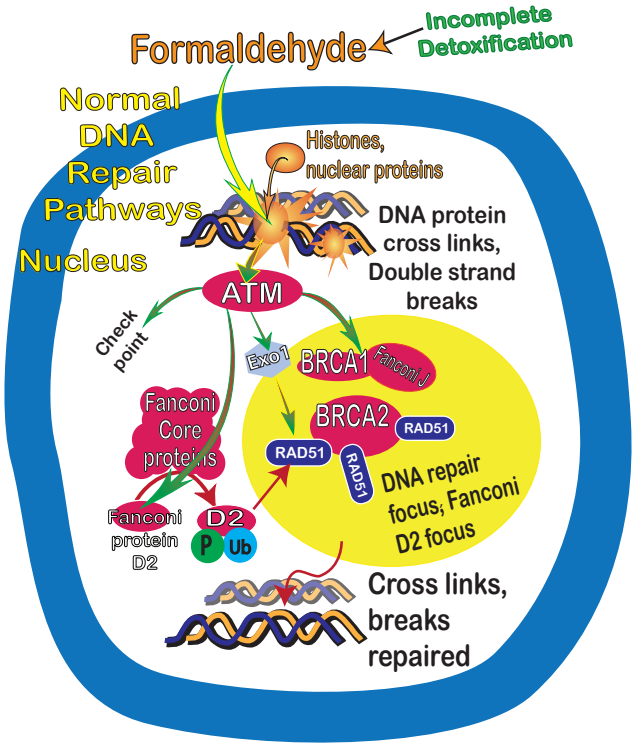

Figure 3 - BRCA1 and BRCA2 in pathways to repair DNA damage caused by formaldehyde and other DNA damaging agents.

BRCA1 and BRCA2 are shown in pathways to correct DNA cross links and double strand breaks caused by formaldehyde. DNA damage is more likely if formaldehyde escapes metabolic detoxification (as shown in Fig. 2). Fanconi proteins and ATM are also shown within these pathways. Hereditary inactivation of a Fanconi gene causes Fanconi anemia, inactivation of the ATM gene causes ataxia-telangiectasia (A-T), and inactivation of BRCA1 or BRCA2 associates with hereditary breast/ovarian cancers. Proteins encoded by genes related to these well known hereditary cancer conditions are colored red [14, 12]. The pathway may be defective in CML and ubiquitin (Ub) is not added to Fanconi protein D2 (see text). Some chemotherapy drugs may have similar effects but data in Table 1 do not support chemotherapy for breast cancer as the major cause of excess AML in mutation carriers.

in BRCA1 are incompatible with human life but heterozygous BRCA1 mutations are well known. Carriers of heterozygous mutations in either BRCA1 or BRCA2 have increased risks for myeloid leukemia Table 1 summarizes risks for myeloid leukemia from 15 studies (A - O) of heterozygous BRCA1/2 mutation carriers or individuals eligible for mutation testing. 12 of the 15 studies reported risks for leukemia or myeloid leukemia that are elevated by at least 50%. Risks may be even greater because none of the 15 studies included populations that had all tested positive for mutation and data was not corrected for mortality.

Test 2. Mutations in other genes encoding the BRCA1/2 pathway (Fig. 3) are associated with myeloid leukemia and would prevent correct repair of formaldehyde damage. Other hereditary cancer related conditions are also associated with homozygous or biallelic mutations in genes encoding proteins within the model pathway (Fig. 3). These conditions are Fanconi anemia caused by inactivation of one of 13 Fanconi anemia genes and ataxia-telangiectasia (A-T) caused by inactivation of the ATM gene.

Mutations in Fanconi anemia genes. In Fanconi anemia patients, summary relative risks for AML were 703.3 [363.7–1354.5] [21]. This suggests that functional Fanconi proteins are essential to prevent AML [24]. Few stringent genotype–phenotype connections have emerged for Fanconi anemia. This suggests other genes and environmental factors modify the phenotype [25].

Mutations in Fanconi genes contribute to a subset of sporadic AML [26-28]. In heterozygous carriers, lymphocytes show increased sensitivity to mutagens, but are not blocked in G2 phase as in full Fanconi Anemia [29,30]. Heterozygous mutation in the Fanconi J gene prevents the encoded helicase from unwinding DNA [31], suggesting one mechanism.

Other relationships exist between leukemias and the pathway in Fig 3. A characteristic fusion protein (BCR/ABL) is found in AML (and in CML) that interferes with the formation of nuclear FANCD2 foci (Fig 3), but this interference can be reversed by the ectopic expression of BRCA1[32].

Mutations in the ATM gene (Fig. 3) may increase risks for myelod leukemias. In addition to requiring BRCA and Fanconi proteins, complex DNA damage (and replication fork stalling) also activate ATM (Fig. 3). ATM modulates the loading of recombinational repair proteins onto translocation breakpoint hotspots. This protects against inappropriate recombination and translocations characteristic of myeloid leukemias [33]. The checkpoint in Fig. 3 stabilizes the genome by stopping the cell cycle so that cells with damaged DNA can complete repairs. In AML, activated ATM fails to engage this checkpoint [34]. There are isolated reports of AML associated with ATM mutation.

Test 3. Formaldehyde causes some DNA damage that requires the pathway in Fig. 3. Many studies show mutations in BRCA1/2 dependent pathways compromise repair of DNA damage from cross-linking agents. Laboratory experiments with cells show that formaldehyde is one of these cross-linking agents. Repairing the complex DNA damage it causes requires BRCA1, BRCA2 (Fanconi protein D1), and 13 other Fanconi proteins (Fig. 3) [13].

DNA-protein cross-links exhibit a dose-response relationship to formaldehyde exposure in the respiratory tract of laboratory animals at exposure concentrations relevant to human exposures. In peripheral white blood cells of occupationally exposed workers, DNA-protein cross-links increased significantly vs controls and had a linear relationship with years of exposure [35].

BRCA1/2 related pathways also partici-

Table 1 Risks of leukemia and oral cavity cancers as cancers following breast, ovarian or fallopian tube cancer in proven or potential BRCA1/2 mutation carriers

Reference number and Study population	Mutation test status	Risk measurement for leukemias [Confidence interval]	Risk for pharynx, sinus or nose cancer
6 children with biallelic BRCA2 mutations [25].	Biallelic BRCA2 mutations (compound heterozygotes)	All developed leukemia at median age 2.2 years. 4 of 6 AMLs	
Review of 27 biallelic BRCA2 mutation patients [26].	Biallelic BRCA2 mutations (compound heterozygotes)	79% cumulative probability of leukemia (primarily AML) by age 10 years	22 oropharyngeal cancers in 59 patients
A. First breast cancer age <45 in 6958 Connecticut women.	Potential mutation carriers eligible for mutation testing	Acute non-lymphocytic leukemia as 2nd cancer O/E=2.9 at 1-4 years and 6.4 at 5-9 years	1.9 (buccal cavity, pharynx)
B. 279,745 primary breast cancer patients, age 35-49, Finnish Cancer Registry (1953-1979)	Potential mutation carriers eligible for mutation testing	Subsequent leukemia (excluding CLL) RR= 3.21 p<.01	NR
C. 82,520 Women with breast cancer age <=45 in 13 cancer registries.	Potential mutation carriers eligible for mutation testing	Myeloid Leukemia SIR = 3.02 (2.32–3.85) Leukemia SIR = 2.16 (1.78–2.59).	1.40 [1.21–1.61]
D. Female breast cancer in Denmark (1943-80) surviving >= 10 years (selects 11,273 younger surviving patients).	Potential mutation carriers eligible for mutation testing	Acute non-lymphocytic leukemia as a 2nd cancer RR=2.3	+#
E. 2,084 Women with primary fallopian tube cancer .	Probable BRCA1/2 mutation carriers.	Non-lymphoid leukemia RR=3.7 (1.0-9.4)	1.4 [1.1–1.6]
F. Women with 2 breast or ovarian cancers in Thames Cancer Registry .	Potential BRCA1/2 mutation carriers eligible for mutation testing	Myeloid leukemia RR=5.04 [1.85-11.0]	14.7 [1.73 -51.6]
G. 2nd cancer after Breast Cancer<50.	Potential BRCA1/2 mutation carriers eligible for mutation testing	Myeloid leukemias RR=2.31 [1.52-3.51]	0.96
H. 2nd cancer after male breast cancer at 1-9 yrs of follow up.	Men at high risk for being (BRCA2) mutation carriers eligible for mutation testing	Myeloid leukemia 3.98 [1.46 – 8.67]	1.25 [0.50 – 2.57]
I. 291 first degree relatives of BRCA1 probands with ovarian cancer	Tested BRCA1 heterozygotes or potential carriers eligible for testing	Leukemias, lymphomas, etc RR=3.7 (1.5 to 9.5) (2006); RR= 2.6 [1.02-6.6] (2001).	NR
J. 11 BRCA1+BRCA2 mutation carriers.	Known BRCA1 and BRCA2 mutation carriers	20% (2/11) leukemias as 2nd primary in 1 BRCA1 and 1 BRCA2 carrier.	+*
K. 3678 women, 50 men 1st degree relatives of mutation carriers or of breast or ovarian cancer patients	471 BRCA2 carriers, 390 noncarriers, and 2186 unknown BRCA2 carrier status	Leukemia RR= 1.12 [0.30–4.25]	2.26 [1.09-4.58]
L. 11847 individuals from 699 families segregating a BRCA1 mutation .	18.9% (2245) tested BRCA1 carriers, 9.3% (1106) tested negative, 71.7% (8496) untested.	Leukemia RR = 0.88 [0.37 to 2.14] p=.83	+**
M. 1811 male and female family members.	50% probability BRCA2 mutation from 139 BRCA2 families.	Leukemia RR= 1.5 [0.5 to 3.5]	2.4
N. 728 individuals male and female	From families with an identified BRCA2 mutation with and without breast cancer history	Acute leukemia 1.54 [0.04±8.59]	Oral cavity 4.17 [0.11±23.26]
O. 1145 individuals male and female	From BRCA1-associated families	Acute leukemia 1.01 [0.03±5.62]	NR

Studies listed in Table 1

A. *Harvey EB and Brinton LA. Second cancer following cancer of the breast in Connecticut, 1935–1982. Natl Cancer Inst Monogr 1985; 68, 99–109*

B. *Mellemkjaer L, Friis S, Olsen JH, Scélo G, Hemminki K, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Kee-Seng C, Pompe-Kirn V, Martos C, Jonasson JG, Boffetta P, Brennan P. Risk of second cancer among women with breast cancer. Int J Cancer 2006; 118(9):2285-92.*

C. *Riska A, Pukkala E, Scélo G, Mellemkjaer L, Hemminki K, Weiderpass E, McBride ML, Pompe-Kirn V, Tracey E, Brewster DH, Kliewer EV, Tonita JM, Kee-Seng C, Jonasson JG, Martos C, Boffetta P, Brennan P. Second primary malignancies in females with primary fallopian tube cancer. Int J Cancer 2007; 120(9):2047-51.*

D. *Evans H., Lewis, C., Robinson, D. et al. Cancer risks in women with 2 breast or ovarian cancers: clues to genetic cancer susceptibility. Int J. Cancer 2001; 94: 758-9*

E. *Evans H, Lewis C, Robinson D, Bell C, Moller H, Hodgson S. Incidence of multiple primary cancers in a cohort of women diagnosed with breast cancer in southeast England. Brit J Cancer 2001; 84: 435-440*

F. *Hemminki K, Scélo G, Boffetta P, Mellemkjaer L, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride M, Kliewer EV, Chia KS, Pompe-Kirn V, Martos C, Jonasson JG, Li X, Brennan P. Second primary malignancies in patients with male breast cancer. Brit. J. Cancer 2005; 92 : 1288-92.*

G. *Teppo L, Pukkala E and Saxen E. Multiple cancer – an epidemiological exercise in Finland. J Natl Cancer Inst 1985; 75: 207–217.*

H. *Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Fan I, Tang J, Li S, Zhang S, Shaw PA, Narod SA. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst. 2006; 98(23):1694-706.*

I. *Risch H, McLaughlin J, Cole D, Rosen B et al. Prevalence of Germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. Am J Hum Genet 2001; 68, 700-710.*

J. *Ewertz, M. & Mouridsen, H. Second cancer following cancer of the female breast in Denmark, 1943-80. Natl Cancer Inst Monogr. 1985; 88:325-9*

K. *Shih H, Nathanson K, Seal S, Collins N, Stratton M, Rebbeck T and Weber B. BRCA1 and BRCA2 mutations in breast cancer families with multiple primary cancers. Clin Cancer Res 2000; 6, 4259-64.*

L. *The Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. J. Natl Cancer Inst. 1999; 91: 1310-1316.*

M. *Thompson D, Easton DF; Breast Cancer Linkage Consortium. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94(18):1358-65*

N. *van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, Vasen HF, Ausems MG, Menko FH, Gomez Garcia EB, Klijn JG, Hogervorst FB, van Houwelingen JC, van't Veer LJ, Rookus MA, van Leeuwen FE; Netherlands Collaborative Group on Hereditary Breast Cancer (HEBON). Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 2005;42(9):711-9.*

O. *Johannsson O, Loman N, Moller T, Kristoffersson U, Borg A, Olsson H. Incidence of malignant tumors in relatives of BRCA1 and BRCA2 germ-line mutation carriers. Eur J Cancer 1999;35:1248–57*

*NR= Not reported. Confidence intervals are given in brackets. #RR=1.1 for mouth cancer. * Head/neck and vocal cord cancer reported as "other primary tumors." ** Nasal sinus cancer reported but RR=0.15 for buccal cavity and pharynx cancer.*

pate in preventing formaldehyde related collateral DNA damage. This includes increased cell proliferation (which increases the probability that damaged cells will multiply and acquire further errors), bone marrow toxicity and immunosuppression (which can reactivate latent viral infections), and inflammation (which can produce cross-links due to oxidative damage).

Test 4. Pharynx associated cancers in mutation carriers. Formaldehyde is implicated in very rare nasopharyngeal and sinonasal cancers [3,6]. The annual incidence of nasal tumors in the United States is < 1 in 100,000 people per year. Such rare outcomes are difficult to study due to a lack of statistical power.

Nasal sinus cancer occurred among 2245 known BRCA1 carriers and 8496 untested relatives(Table 1, study L). Two "nose cancers" were found among 471 known heterozygous BRCA2 carriers and 2186 untested family members. (Table 1, study K) One of two buccal cavity cancers in 1160 relatives of A-T patients was nasopharyngeal cancer in a 6 year old[36]. In addition to causing cancer itself, formaldehyde might facilitate human papilloma virus (HPV) infections by damaging both the epithelial barrier and immunity. HPV infection has been implicated in oropharyngeal cancer, a site where nasal sinus cancer originates. The gene for the formaldehyde scavenger ADH3 may even be lost in HPV associated tumors [37].

Computational models predict the nose absorbs approximately 90% of inhaled formaldehyde at resting inspiration. The exposure of oral cavity structures to formaldehyde markedly increases during heavy exercise, [38] as breathing shifts to oral. Cancers of the oral cavity are the most frequent solid tumors in Fanconi homozygotes with relative risk >200 times normal [23, 21]. For heterozygotes or potential heterozygotes (Table 1), most studies report some increase in risks for cancers within the oral cavity.

Different incidences of cancers linked to formaldehyde in different environments. Geographic variation in nasopharyngeal carcinoma reflects a complex etiology of several subtypes. It is not currently possible to separate environmental, viral (Epstein Barr virus), and genetic components as first or second hits. High to intermediate rates in endemic areas contrast markedly with the uniformly rare rates seen in most of the world [39]. Leukemia rates also differ substantially for different racial and ethnic groups living exposed to different levels of environmental formaldehyde. Leukemia incidence is lowest among American Indians/Alaskan natives (6.5 per 100,000).

Test 5. Comparisons of chromosome abnormalities. Greater numbers of DNA-protein cross-links were found in breast cancer patients than in matched controls [40] and formaldehyde has been positively associated with breast cancer risk [41]. It is well known that BRCA1/2 related pathways help protect against chromosome losses. 81% of BRCA1 deficient breast tumors lose chromosome 4q [11]. Similarly 40% of BRCA1 deficient breast cancers have lost chromosome 12q [11]. These losses were much more common than in control tumors. The human alcohol dehydrogenase genes essential for formaldehyde detoxification are found in a cluster on chromosome 4q, and ALDH2 is found on chromosome 12q (Fig. 2). Loss of either chromosome 4q or 12q destroys genes for the main protective metabolic pathways (Fig. 2) that protect against formaldehyde. Either loss then may accelerate latent and occult breast tumors.

Fanconi anemia patients with AML and myelodysplastic syndrome commonly lose one copy of chromosome 7. Formaldehyde exposure associates with chromosome 7 loss in the stem/progenitor cells where leukemia may originate [1].

Losses of genetic material from chromosome 5 and chromosome 7 common in myeloid leukemias are also associated with hereditary breast cancers. 86% of BRCA1 associated breast

tumors lost chromosome 5q [11] and 27% of BRCA2 breast cancers lost a marker on chromosome 7 [42]. The inherited gene defects may also facilitate loss of one copy of chromosome 17, containing BRCA1 and p53 genes. In myeloid leukemias, chromosome 17 is frequently lost or involved in complex chromosomal abnormalities including balanced translocations involving the BRCA1 locus [43]. These observations suggest some pathogenic mechanisms in leukemias may be related to those in hereditary breast cancers.

Test 6. Treatment related risk factors for myeloid leukemia. In the studies in Table 1, most of the excess risk for AML is probably not due to therapy for breast cancer. AML occurs with virtual certainty in children and infants with biallelic mutations in BRCA2. AML also occurs at very young ages in Fanconi anemia patients, before any chemotherapy or radiation has been given. Moreover defects in pathways requiring normal BRCA gene function are associated with other hematopoietic malignancies that are not generally considered to be therapy related [21].

The first chemotherapy regimen for breast cancer was not published until 1975 with large trial results appearing in 1976 [44]. The first three studies in Table 1 include patients diagnosed with breast cancer before adjuvant chemotherapy became widely used. In comparison to later studies, the three pre-chemotherapy studies in Table 1 do not show less risk for AML. In one early study, women over 55 had no excess risk for any second cancer while women younger than 55 still had over 3 times the risk for myeloid leukemia [Table 1 Study A]. Neither group was unlikely to receive routine chemotherapy. The observation of approximately the same risk for AML before and after 1975 is not compatible with the fact that chemotherapy was given to a larger proportion of breast cancer patients during later periods [Table 1, Study C].

A few of the more recent studies in Table 1 show no excess risk for myeloid leukemia, consistent with environmental or additional genetic variation. Relative risks for myeloid leukema if platinum chemotherapy was likely to be used are not substantially higher (Table 1, studies E and F). Moreover both studies E and F reported elevated risks for cancers of the pharynx region, perhaps related to inhalation or facilitated HPV infection.

Radiation therapy. Therapeutic doses of targeted field radiation causes very little or no increased risk of myeloid cancers. This is consistent with myeloid stem cells being more radiation resistant than non-stem cells [45, 46].

Despite younger ages, breast cancer patients with BRCAI/2 mutations present at a similar stage, display a normal acute reaction to radiotherapy and have a similar prognosis compared to sporadic breast cancer patients [47]. An increased risk of radiation therapy related-AML is largely confined to young women with stage III breast cancer, (spread to lymphoid tissue). These patients are more likely to receive radiation in some combination with cytotoxic chemotherapy. In stage I disease, radiation is given alone and there is very little excess risk for AML [48]. Nonetheless sound arguments remain to limit radiation exposure in mutation carriers.

Other inherited cancer associated conditions and environmental carcinogens.

Table 2 gives additional examples of inherited cancer associated conditions that have increased susceptibility to environmental carcinogens. Common findings are increased sensitivity to cancer associated infections, to radiation, and to chemical carcinogens. This shows that the phenomenon of increased sensitivity to the environmental carcinogen formaldehyde is probably representative of a broad general phenomenon. Further studies of the relationship between

genetic inheritance and environmental cancer susceptibility are needed.

Clinical Significance

Genetic conditions affect susceptibility to carcinogens. Avoiding specific mutagens that crosslink DNA may reduce cancer risk for those with mutations affecting BRCA1/2 pathways. Activity of alcohol and aldehyde dehydrogenase enzymes should further stratify risk. Other common DNA damaging agents [benzopyrene, hexavalent chromium, etc] might also cause undue cancer risks. Identifying distinct environmental hazards may prevent other hereditary cancer conditions.

Table 2. Examples of hereditary cancer syndromes with known sensitivity to specific environmental carcinogens.

Major hereditary tumor types, organ	Gene / Pathway	Hereditary Syndrome(s)	Examples of known or suspected risk factors, carcinogens, pathogens, inflammation, infection
Colon, thyroid, stomach intestine	APC /APC	FAP	Increased sensitivity to viral transformation [1] Viral proteins strongly promote hepatoblastoma [2] (750 - 7500 times normal risk with most before age 3 years. Increased risk for medulloblastoma with polyoma virus JCV [3]. Anti-inflammatory drugs reduce number and size of polyps.
Colon	MUTYH / BER	Polyposis	Oxidizing agents in colon. Defect linked to repair of oxidized guanine in DNA (8-oxoguanine DNA)[4]
Colon uterus	MSH2, MLH1, MSH6, PMS2 / MMR	HNPCC	Inflammation (Anti inflammatories markedly reduce risk)[5], cigarette smoking [6].
Small Intestine, stomach, colon ovary, pancreas	STK11 (LKB1)/ PI3K	Peutz-Jeghers syndrome	Increased sensitivity to viral transformation [1] Mutations involved in a subset of HBV related hepatocellular carcinoma [7]
Thyroid, breast, gliobastoma, melanoma, prostate carcinoma, endometrial carcinoma	PTEN	Bannayan-Riley-Ruvalcaba syndrome, Bannayan-Zonana syndrome, Riley-Smith syndrome, Ruvalcaba-Myhre-Smith syndrome, Macrocephaly, Pseudopapilledema, Multiple hemangiomata, Macrocephaly, Multiple lipomas, Hemangiomata	PTEN is targeted by cancer associated pathogens HCV, HBV, HPV and h.pylori.
Skin, medulloblastoma	PTCH /GLI or SUFU /GLI	Gorlin syndrome, Medulloblastoma predisposition	The human polyomaviruses JC virus (JCV) is associated with glial tumors and pediatric medulloblastomas [8,3] Report of thousands of tumors appearing after radiation therapy[9]

Major hereditary tumor types, organ	**Gene / Pathway**	**Hereditary Syndrome(s)**	**Examples of known or suspected risk factors, carcinogens, pathogens, inflammation, infection**
Malignant melanoma basal cell and squamous cell carcinoma	XPA, C; ERCC2–5; DDB2 /NER	Xeroderma pigmentosum	UV light
Lymphomas, leukemias, solid tumors, breast cancers,	A-T, NBS, DNA 13 FA genes including BRCA2, BRCA1	Ataxia telangiectasia Nijmegan breakage syndrome, Fanconi anemia, Fanconi pancytopenia	Infection/inflammation, DNA crosslinking agents such as mitomycin, acetaldehyde from alcohol metabolism. Early radiation exposure from chest x-rays in BRCA1 carriers is a risk factor for breast cancer [10].
Lymphomas	Fas gene, Fas receptor, caspase 10, 8 genes, cyclin D1, ATM	Chronic lymphoproliferative disorder, Wiskott-Aldridge, common variable immunodeficiency, A-T	Immunosuppressive treatments. HIV, HHV8, EBV, HTLV, h.pylori infection Agricultural, petrochemical, firefighting occupation.
Leukemias, lymphomas, HNSCC, breast cancer, carcinomas and broad spectrum of cancers	recQ helicase	Bloom syndrome	Sun, radiation, papilloma virus infection, carcinogens including tobacco, alcohol
AML, juvenile myelomonocytic leukemias, neuroblastoma, melanoma, , breast cancer, lung cancer, colorectal cancer.	PTPN11, codes for phosphatase Shp2	LEOPARD syndrome, NOONAN syndrome, Cardiocutaneous syndrome, Multiple-lentigines syndrome	Deregulates response to inflammatory cytokines. Viral infections present in 2/3 of children with juvenile myelomoncytic leukemia at diagnosis [11] SHP2 may serve as part of an initial protective mechanism against UV skin carcinogenesis [12]
Thyroid, melanoma, soft tissue sarcoma Osteosarcoma	WRN/CIN helicase? belonging to recQ family	Werner Syndrome	Human herpesvirus 8 [Kaposis sarcoma] Sarcomas often start in areas of the body that had been treated with radiation. Fibroblasts are unusually sensitive to the DNA damaging agent 4-nitroquinoline 1-oxide [13]
Leukemias	CBP/p300	Broad thumb hallux syndrome, Rubinstein-Taybi syndrome	Many viral oncoproteins have been found to modulate p300/CBP function. These include Ad E1a, SV40 LT, HPV E6, HPV E7, EBV EBNA2, HTLV Tax and HIV Tat[14]

Major hereditary tumor types, organ	Gene / Pathway	Hereditary Syndrome(s)	Examples of known or suspected risk factors, carcinogens, pathogens, inflammation, infection
Osteosarcoma, skin cancer	RECQL4 helicase	Rothmund Thompson syndrome	Sites of bone infarcts, metallic prostheses and prior internal fixation. Ionizing radiation, intravenous radium and Thorotrast. Alkylating agents may also contribute, apparently independent of radiotherapy [15].
CNS hemangioblastomas; renal cell carcinomas; pheochromocytomas; pancreatic islet cell tumors; endolymphatic sac tumors.	VHL / HIF1	Von Hippel–Lindau syndrome	High-level exposure to trichloroethylene and reactive metabolites are genotoxic to kidney proximal tubule. This is a tumor-initiating process linked with mutational changes in the VHL tumor suppressor gene [16]
Wilms' kidney	WT1 /p53	Familial Wilms tumor	Hair coloring products, vaginal infections, tea drinking, prenatal pesticides.
Breast, sarcoma, adrenal, brain.	TP53 (p53)/ p53	Li-Fraumeni syndrome	Virtually all DNA tumor viruses that cause tumors in experimental animals or humans encode proteins that inactivate both Rb and p53 [17]
Eye	RB1 /RB	Hereditary retinoblastoma	Virtually all DNA tumor viruses that cause tumors in experimental animals or humans encode proteins that inactivate both Rb and p53 [17]

Footnotes to Table 2

1. Miyaki M, Akamatsu N, Rokutanda M, Ono T, Yoshikura H, Sasaki M, Tonomura A, Utsunomiya J. Gann. 1980 Dec;71(6):797-803.
2. Kim DJ, Tremblay ML, Digiovanni J. Protein tyrosine phosphatases, TC-PTP, SHP1 and SHP2 cooperate in rapid dephosphorylation of Stat3 in keratinocytes following UVB irradiation, 2010)
3. Krynska B, Del Valle L, Croul S, Gordon J, Katsetos CD, Carbone M, Giordano A, Khalili K. Detection of human neurotropic JC virus DNA sequence and expression of the viral oncogenic protein in pediatric medulloblastomas. Proc Natl Acad Sci U S A. 1999 Sep 28;96(20):11519-24.
4. David SS, O'Shea VL, Kundu S. (2007) Base-excision repair of oxidative DNA damage. Nature. 447(7147):941-50.
5. Burn J, Gerdes A, Mecklin J.P., et al. Aspirin prevents cancer in Lynch syndrome. Eur J Cancer Supplements 2009; 7: 320
6. Yang F, Jin C, Fu D. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. N Engl J Med. 2009;360(14):1461-2;
7. Kim CJ, Cho YG, Park JY,, et al. Genetic analysis of the LKB/STK11 gene in hepatocellular carcinomas. Eur. J Cancer 2004; 40:136-41.
8. Damania B. DNA tumor viruses and human cancer. Trends Microbiol. 2007;15(1):38-44.
9. Walter AW, Pivnick EK, Bale AE, Kun LE. Complications of the nevoid basal cell carcinoma syndrome: a case report. J Pediatr Hematol Oncol. 1997 May-Jun;19(3):258-62.
10. Gronwald J, Pijpe A, Byrski T, Huzarski T, Stawicka M, Cybulski C, van Leeuwen F, Lubiński J, Narod SA. Early radiation exposures and BRCA1-associated breast cancer in young women from Poland. Breast Cancer Res Treat. 2008;112(3):581-4.

11. Manabe A., Yoshimasu T, Ebihara Y, et al. Viral infections in juvenile myelomonocytic leukemia: prevalence and clinical implications. J Pediatr Hematol Oncol, 2004; 26: 636-641.
12. Kim. Protein tyrosine posphatases, TC-PTP, SHP1 and SHP2 cooperate in rpaid dephosphorylation of Stat3 in heratinocytes following UVB irradiation. PLos One 2010; 5:e10290.
13. Prince PR, Ogburn CE, Moser MJ, Emond MJ, Martin GM, Monnat RJ Jr. Cell fusion corrects the 4-nitroquinoline 1-oxide sensitivity of Werner syndrome fibroblast cell lines. Hum Genet. 1999; 105(1-2):132-8.
14. Bernat A, Avvakumov N, Mymryk JS, Banks L. Interaction between the HPV E7 oncoprotein and the transcriptional coactivator p300. Oncogene. 2003; 22(39):7871-81.
15. Ottaviani G, Jaffe N. The etiology of osteosarcoma. Cancer Treat Res. 2009;152:15-32.
16. Brüning T, Bolt HM. Renal toxicity and carcinogenicity of trichloroethylene: key results, mechanisms, and controversies. Crit Rev Toxicol. 2000;30(3):253-85.
17. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. Nat Med. 2004;10(8):789-99

References

1. Zhang L, Tang X, Rothman N, Vermeulen R, Ji Z, Shen M, Qiu C, Guo W, Liu S, Reiss B, Freeman LB, Ge Y, Hubbard AE, Hua M, Blair A, Galvan N, Ruan X, Alter BP, Xin KX, Li S, Moore LE, Kim S, Xie Y, Hayes RB, Azuma M, Hauptmann M, Xiong J, Stewart P, Li L, Rappaport SM, Huang H, Fraumeni JF Jr, Smith MT, Lan Q: Occupational exposure to formaldehyde, hematotoxicity, and leukemia-specific chromosome changes in cultured myeloid progenitor cells. Cancer Epidemiol Biomarkers Prev. 2010: 19(1):80-8.
2. Agency for Toxic Substances and Disease Registry, Division of Toxicology and Environmental Medicine, Atlanta, GA 30333. 2010. Addendum to the Toxicological Profile for Formaldehyde.
3. Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V; WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens--Part F: chemical agents and related occupations. *Lancet Oncol.* 2009; **10**(12):1143-4.
4. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. July 1999. Toxicological profile for Formaldehyde.
5. Hauptmann M, Stewart PA, Lubin JH, Beane Freeman LE, Hornung RW, Herrick RF, Hoover RN, Fraumeni JF Jr, Blair A, Hayes RB. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. J Natl Cancer Inst. 2009; 101(24):1696-708
6. National Toxicology Program. Final Report on Carcinogens. Background Document for Formaldehyde. Rep Carcinog Backgr Doc. 2010; (10-5981):i-512.
7. Bei JX, Li Y, Jia WH, Feng BJ, Zhou G, Chen LZ, Feng QS, Low HQ, Zhang H, He F, Tai ES, Kang T, Liu ET, Liu J, Zeng YX. A genome-wide association study of nasopharyngeal carcinoma identifies three new susceptibility loci. Nat. Genet. 2010; 42(7):599-603.
8. Lu K, Ye W, Zhou L, Collins LB, Chen X, Gold A, Ball LM, Swenberg JA. Structural characterization of formaldehyde-induced cross-links between amino acids and deoxynucleosides and their oligomers. J Am Chem Soc. 2010: 132, 3388–3399
9. Teng S, Beard K, Pourahmad, J, et al. The formaldehyde metabolic detoxification enzyme systems and molecular cytotoxic mechanism in isolated rat hepatocytes. Chem Biol Interact 2001; 130–132:285–296.
10. Lu K, Moeller B, Doyle-Eisele M, McDonald J, Swenberg JA. Molecular Dosimetry of N(2)-Hydroxymethyl-dG DNA Adducts in Rats Exposed to Formaldehyde. Chem Res Toxicol. Feb 2011;18;24(2):159-61.
11. Tirkkonen M, Johannsson O, Agnarsson B, Olsson H, et al Distinct Somatic Genetic Changes Associated with Tumor Progression in Carriers of BRCA1and BRCA2 Germ-line Mutations Cancer Research 1997;57, 1222-1227.
12. Friedenson B. A theory that explains the tissue specificity of BRCA1/2 related and other hereditary cancers. J. Med. Med. Sci. 2010; 1(8): 372-384
13. Nakano T, Katafuchi A, Matsubara M, Terato H, Tsuboi T, Masuda T, Tatsumoto T, Pack SP, Makino K, Croteau DL, Van Houten B, Iijima K, Tauchi H, Ide H. Homologous recombination but not nucleotide excision repair plays a pivotal role in tolerance of DNA-protein cross-links in mammalian cells. J Biol Chem. 2009; 284(40):27065-76.
14. D'Andrea AD, Grompe M. The Fanconi anaemia/BRCA pathway. Nat Rev Cancer. 2003;3(1):23-34.
15. Welcsh PL, King MC. BRCA1 and BRCA2 and the genetics of breast and ovarian cancer. Hum Mol Genet. 2001 Apr;10(7):705-13
16. Elledge S and Amon A. The BRCA1 suppressor hypothesis: An explanation for the tissue-specific tumor development in BRCA1 patients Cancer Cell 2002; 1:129-132.
17. Fan, S., Ma, Y.X., Wang, C., Yuan, R.Q., Meng, Q., Wang, J.A., Erdos, M., Goldberg, I.D., Webb, P., Kushner, P.J., et al. Role of direct interaction in BRCA1 inhibition of estrogen receptor activity. Oncogene 2001; 20, 77–87.
18. Friedenson B., 2005. BRCA1 and BRCA2 pathways and the risk of cancers other than breast or ovarian. Medscape General Medicine MedgenMed June 29, 7(2) 2005 Available at http://www.medscape.com/viewarticle/505347.
19. Friedenson B., Inflammatory processes inordinately increase tissue specific cancer risks in carriers of mutations in BRCA1, BRCA2, ATM or Fanconi anemia genes. J. Med. Med. Sci. 2010; 1(8): 356-371
20. Begg C, Haile R, Borg A, Malone K, Concannon P, Thomas D, Langholz B, Bernstein L, Olsen J, Lynch C, Anton-Culver H, Capanu M, Liang X, Hummer A, Sima C, Bernstein J. Variation of Breast Cancer Risk Among BRCA1/2 Carriers JAMA 2008; 299(2):194-201
21. Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer 2007; 7:152.
22. Wagner JE, Tolar J, Levran O, Scholl T, Deffenbaugh A, Satagopan J, Ben-Porat L, Mah K, Batish SD, Kutler DI, MacMillan ML, Hanenberg H, Auerbach AD. Germline mutations in BRCA2: shared genetic susceptibility to breast cancer, early onset leukemia, and Fanconi anemia. Blood 2004; 103(8):3226-9.
23. Alter B, Rosenberg P. Brody L. Clinical and molecular features associated with biallelic mutations in FANCD1/BRCA2. J Med Genet 2007;44:1–9.
24. Tischkowitz MD, Morgan NV, Grimwade D, Eddy C, Ball S, Vorechovsky I, Langabeer S, Stöger R, Hodgson SV, Mathew CG. Deletion and reduced expression of the Fanconi anemia FANCA gene in sporadic acute myeloid leukemia. Leukemia 2004; 18(3):420-5.
25. Neveling K, Endt D, Hoehn H, Schindler D. Genotype-phenotype correlations in Fanconi anemia. Mutat Res. 2009; 668(1-2):73-91.
26. Lensch MW, Tischkowitz M, Christianson TA, Reifsteck CA, Speckhart SA, Jakobs PM, O'Dwyer ME, Olson SB, Le Beau MM, Hodgson SV, Mathew CG, Larson RA, Bagby GC Jr. Acquired FANCA dysfunction and cytogenetic instability in adult acute myelogenous leukemia. Blood 2003;102(1):7-16.
27. Condie A, Powles RL, Hudson CD, Shepherd V, Bevan S, Yuille MR, Houlston RS. Analysis of the Fanconi anaemia complementation group A gene in acute myeloid leukaemia. Leuk Lymphoma. 2002;43(9):1849-53.
28. Xie Y, de Winter JP, Waisfisz Q, Nieuwint AW, Scheper RJ, Arwert F, Hoatlin ME, Ossenkoppele GJ, Schuurhuis GJ, Joenje H. Aberrant Fanconi anaemia protein profiles in acute myeloid leukae-

mia cells. Br J Haematol. 2000; 111(4):1057-64.

29. Rischewski JR, Clausen H, Leber V, Niemeyer C, Ritter J, Schindler D, Schneppenheim R. 2000. A heterozygous frameshift mutation in the Fanconi anemia C gene in familial T-ALL and secondary malignancy. Klin Padiatr. 2000; 212(4):174-6.
30. Mohseni Meybodi A, Mozdarani H. DNA damage in leukocytes from Fanconi anemia (FA) patients and heterozygotes induced by mitomycin C and ionizing radiation as assessed by the comet and comet-FISH assay. Iran Biomed J. 2009; 3(1):1-8.
31. Wu Y, Brosh RM Jr. Helicase-inactivating mutations as a basis for dominant negative phenotypes. Cell Cycle. 2010;9(20):4080-90.
32. Valeri A, Alonso-Ferrero ME, Río P, Pujol MR, Casado JA, Pérez L, Jacome A, Agirre X, Calasanz MJ, Hanenberg H, Surrallés J, Prosper F, Albella B, Bueren JA. Bcr/Abl interferes with the Fanconi anemia/BRCA pathway: implications in the chromosomal instability of chronic myeloid leukemia cells. PLoS One. 2010 Dec 28;5(12):e15525.
33. Sun J, Oma Y, Harata M, Kono K, Shima H, Kinomura A, Ikura T, Suzuki H, Mizutani S, Kanaar R, Tashiro S. ATM modulates the loading of recombination proteins onto a chromosomal translocation breakpoint hotspot. PLoS One. 2010 Oct 27;5(10):e13554
34. Boehrer S, Adès L, Tajeddine N, Hofmann WK, Kriener S, Bug G, Ottmann OG, Ruthardt M, Galluzzi L, Fouassier C, Tailler M, Olaussen KA, Gardin C, Eclache V, de Botton S, Thepot S, Fenaux P, Kroemer G. Suppression of the DNA damage response in acute myeloid leukemia versus myelodysplastic syndrome. Oncogene. 2009 Jun 4;28(22):2205-18. Epub 2009 Apr 27.
35. Shaham J, Bomstein Y, Meltzer A, Kaufman Z, Palma E, Ribak J. DNA--protein crosslinks, a biomarker of exposure to formaldehyde--in vitro and in vivo studies. Carcinogenesis. 1996; 17(1):121-5.
36. Thompson D, Duedal S, Kirner J, McGuffog L, Last, Reiman J, Byrd P, Taylor M, Easton D. Cancer Risks and Mortality in Heterozygous ATM Mutation Carriers J Natl Cancer Inst 2005; 97: 813-822,
37. Mitra A , Murty V, Li R, et al. Allelotype Analysis of Cervical Carcinoma Cancer Res 1994;54:4481-4487.
38. Kimbell, JS; Overton, JH; Subramaniam, RP; et al. Dosimetry modeling of inhaled formaldehyde: binning nasal flux predictions for quantitative risk assessment. Toxicol Sci 2001; 64:111–121.
39. Bray F, Haugen M, Moger TA, Tretli S, Aalen OO, Grotmol T. Age-incidence curves of nasopharyngeal carcinoma worldwide: bimodality in low-risk populations and aetiologic implications. Cancer Epidemiol Biomarkers Prev. 2008;17(9):2356-65.
40. Wu FY, Lee YJ, Chen DR, Kuo HW. Association of DNA-protein crosslinks and breast cancer Mutat Res. 2002; 501(1-2):69-78.
41. Coyle YM, Hynan LS, Euhus DM, Minhajuddin AT. An ecological study of the association of environmental chemicals on breast cancer incidence in Texas. Breast Cancer Res Treat. 2005; 92(2):107-14.
42. Eiriksdottir G, Barkardottir RB, Agnarsson BA, Johannesdottir G, Olafsdottir K, Egilsson V, Ingvarsson S. High incidence of loss of heterozygosity at chromosome 17p13 in breast tumours from BRCA2 mutation carriers. Oncogene. 1998; 16(1):21-6.
43. Zhu Y, Xu W, Liu Q, Pan J, Qiu H, Wang R, Qiao C, Jiang Y, Zhang S, Fan L, Zhang J, Shen Y, Xue Y, Li J. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. [Abnormalities of chromosome 17 in myeloid malignancies with complex chromosomal abnormalities] 2008; 25(5):579-82
44. DeVita VT Jr, Chu E. A history of cancer chemotherapy. Cancer Res. 2008 68(21):8643-53
45. Pierce LJ, Haffty BG. Radiotherapy in the treatment of hereditary breast cancer. Semin Radiat Oncol. 2011; 21(1):43-50.
46. Diehn M, Cho RW, Lobo NA, Kalisky T, Dorie MJ, Kulp AN, Qian D, Lam JS, Ailles LE, Wong M, Joshua B, Kaplan MJ, Wapnir I, Dirbas FM, Somlo G, Garberoglio C, Paz B, Shen J, Lau SK, Quake SR, Brown JM, Weissman IL, Clarke MF. Association of reactive oxygen species levels and radioresistance in cancer stem cells. Nature. 2009;458(7239):780-3.
47. Gaffney DK, Brohet RM, Lewis CM, Holden JA, Buys SS, Neuhausen SL, Steele L, Avizonis V, Stewart JR, Cannon-Albright LA. Response to radiation therapy and prognosis in breast cancer patients with BRCA1 and BRCA2 mutations. Radiother Oncol. 1998; 47(2):129-36.
48. Martin MG, Welch JS, Luo J, Ellis MJ, Graubert TA, Walter MJ. Therapy related acute myeloid leukemia in breast cancer survivors, a population-based study. Breast Cancer Res Treat. 2009, 118(3):593-8.